

# Waarom worden we allergisch ?

Bart N. Lambrecht, MD, PhD

VIB Inflammation Research Center

Afdeling longziekten, UZGent



# Wat is allergie?

‘Overmatige reactie van het afweersysteem tegen schadeloze stoffen waar een groot deel van de bevolking niet op reageert’

Komt vaak voor samen in één individu of binnen één familie

Dit kan zich uiten als astma, hooikoorts, eczeem, urticaria,....

Soms reageert het afweersysteem tegen schadeloze stoffen



Astma



Hooikoorts

“allergie of overgevoeligheid”

# Eczeem



# Voedingsallergie



## Urticaria na innemen van een antibioticum



# Wat is allergie ?

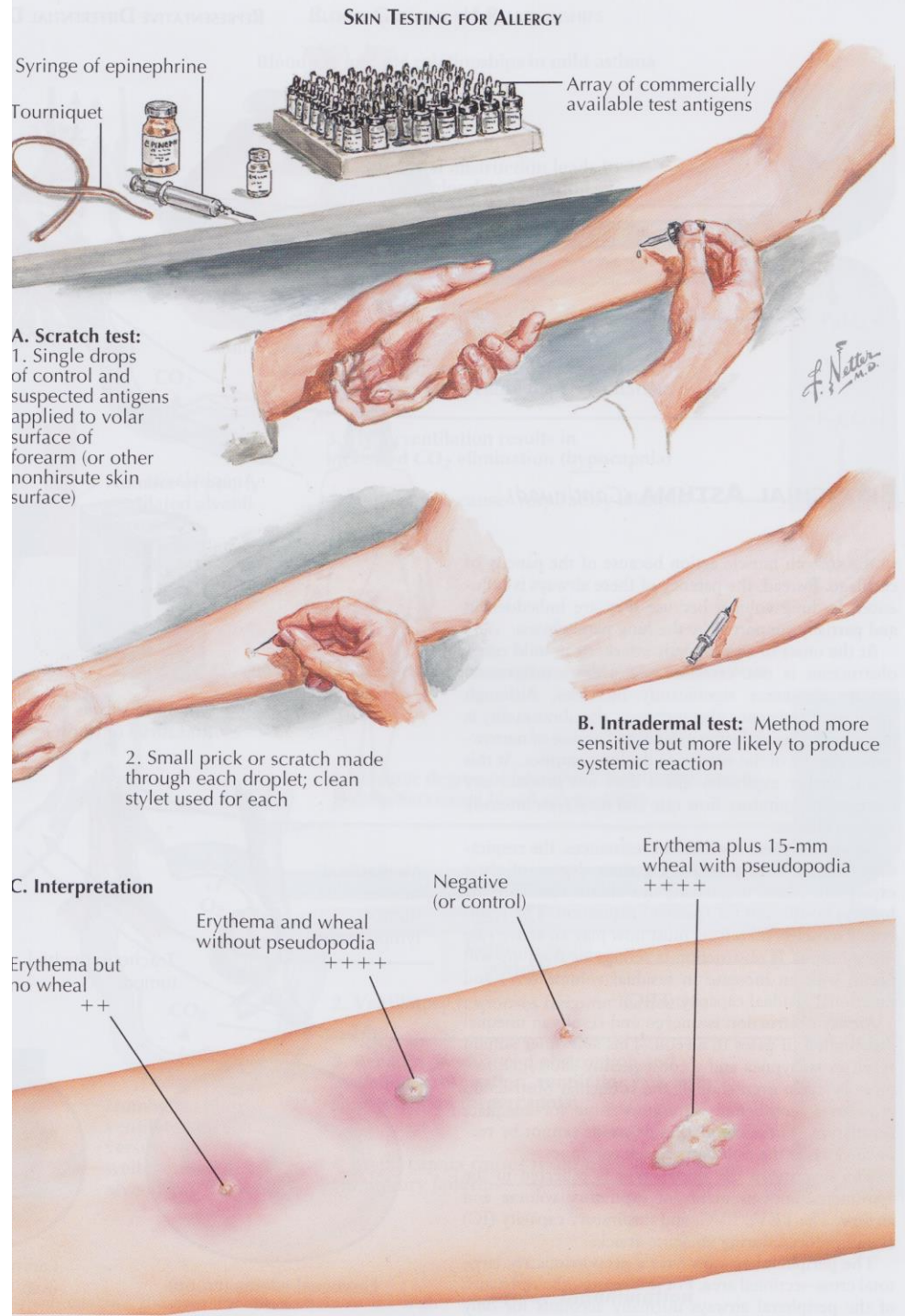
Deels genetisch bepaalde neiging  
tot productie van IgE antistoffen tegen deze  
schadeloze antigenen



# Diagnostiek van allergie

## HUIDTEST

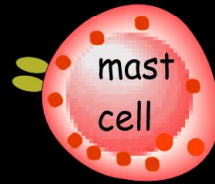
Patiënt moet enkele dagen voordien anti-histaminica stoppen



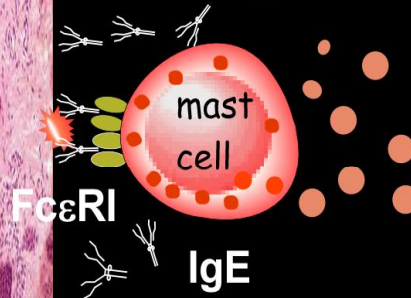
# Hoe werkt de huidtest ?



**Gezond**



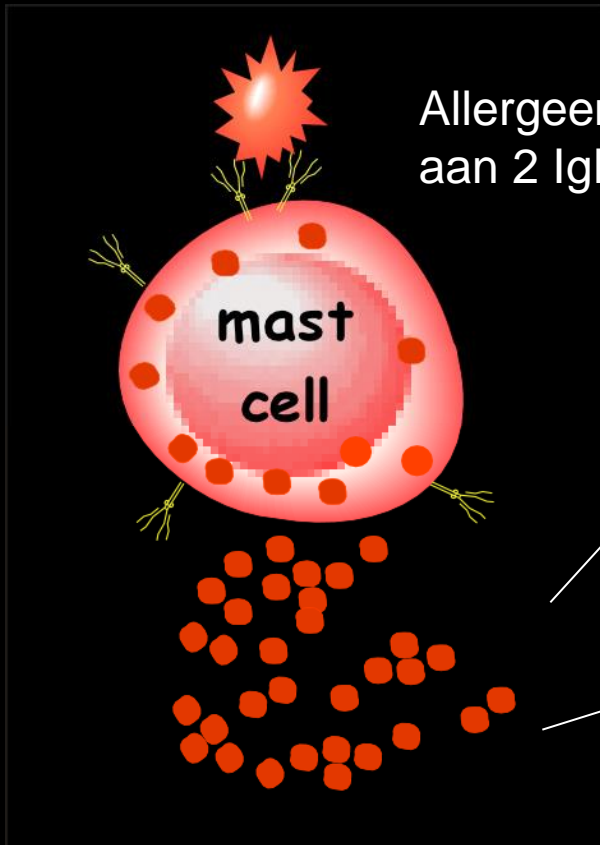
**Allergie**



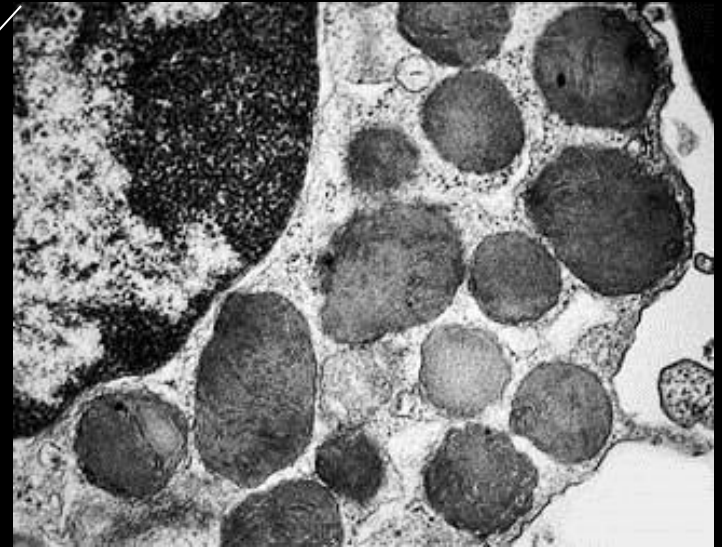
Roodheid en zwelling



# Mest cell



Allergeen bindt  
aan 2 IgE molecules

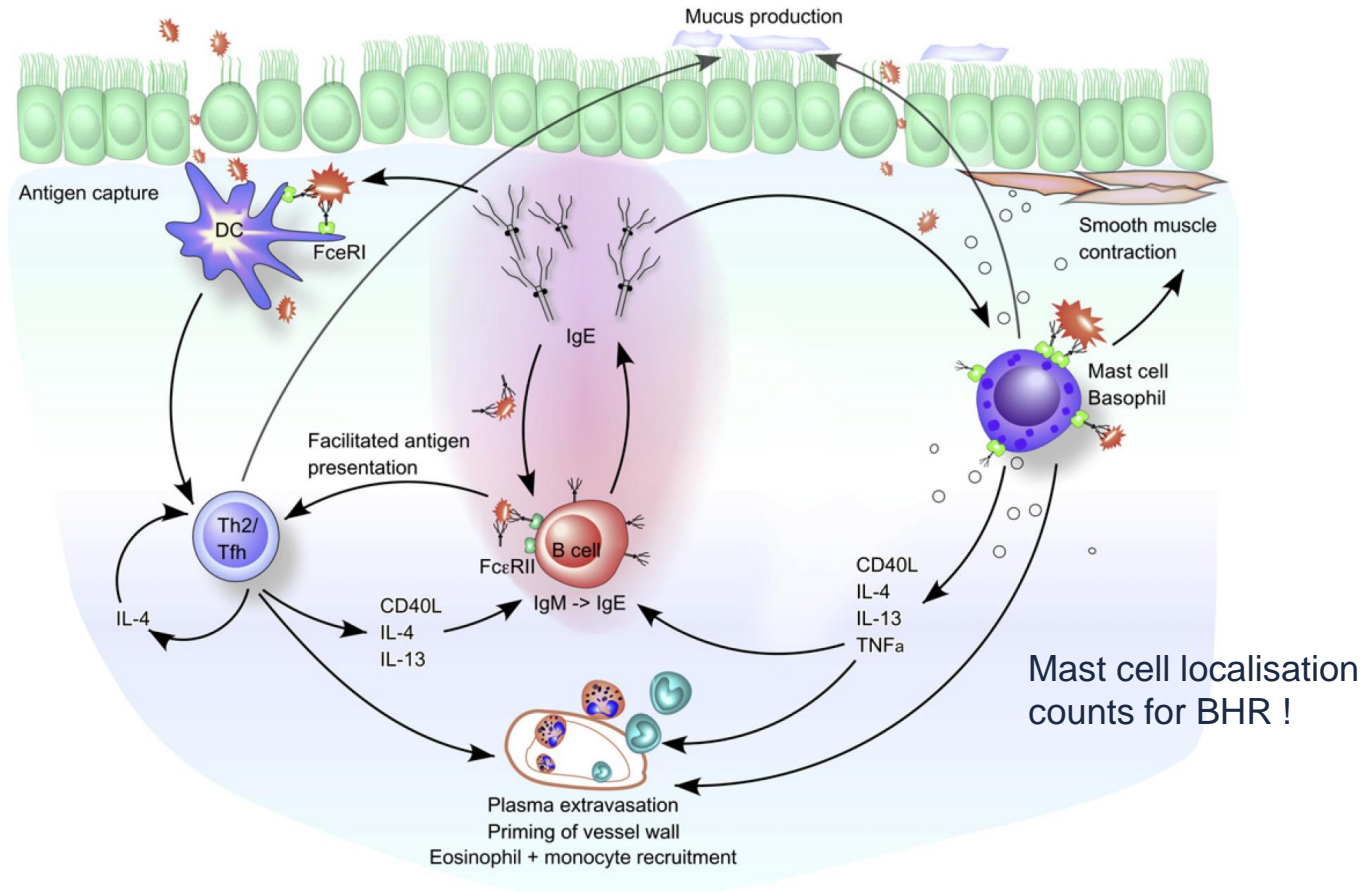


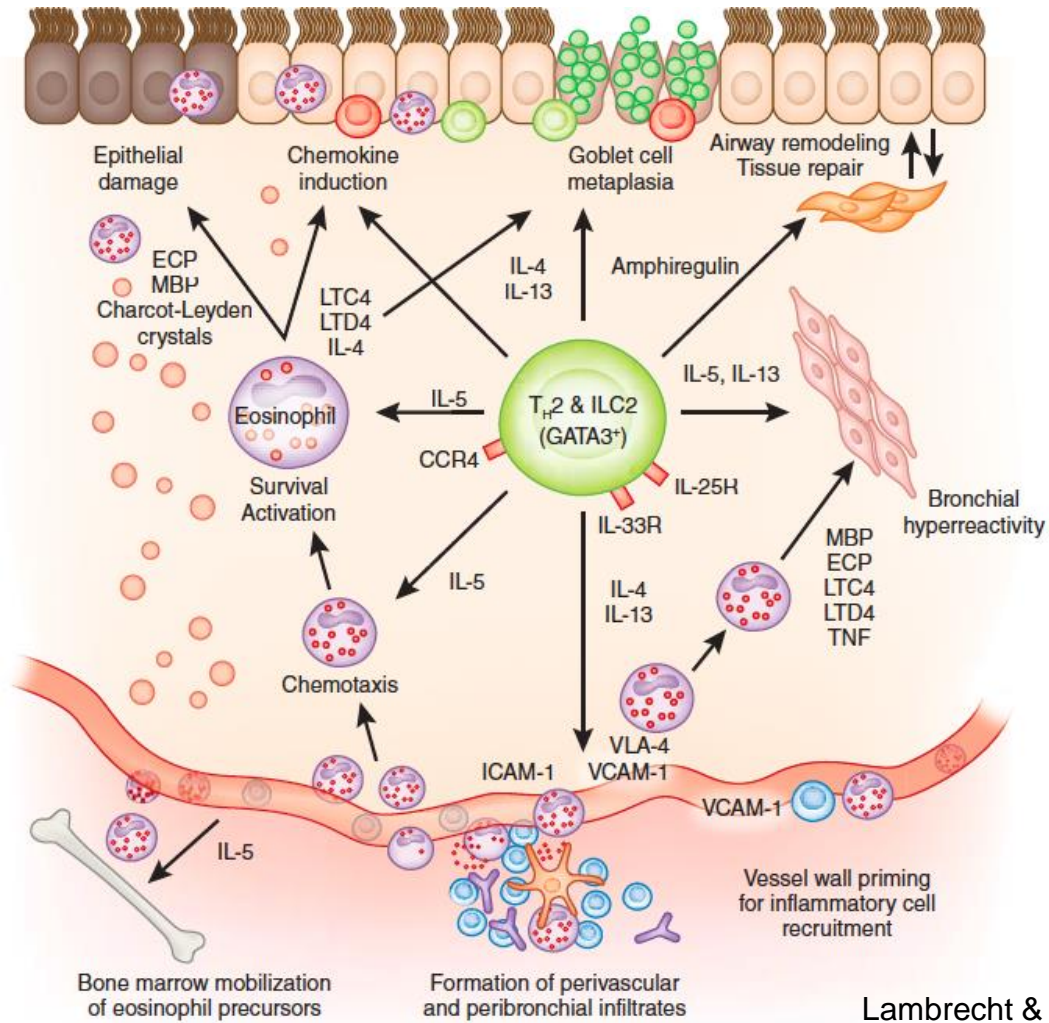
**Granules vol met**

- Histamine
- Leukotriënen ( $\text{LTC}_{4,..}$ )
- ontstekingsstoffen

1. Onmiddellijke vrijstelling ontstekingsstoffen
2. Aanmaak nieuwe ontstekingsstoffen

## The importance of IgE/mast cell/basophil in asthma





Lambrecht & Hammad, *Nat Immunol*, 2015  
 Coquet et al. *Immunity*, 2015

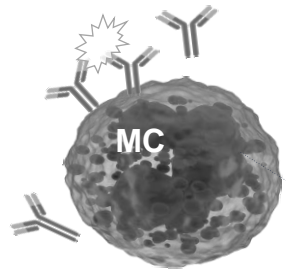


## Type 2 immunity was developed to fight helminths



# Type 2 immunity developed to neutralize venoms

## Mast cell (MC) and basophil (B) functions

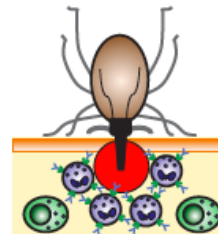


MC proteases  
(degrade venom components)

innate and adaptive immune resistance to venoms (MCs)



Products: histamine, heparin (MCs, not B),  
cytokines, chemokines, growth factors,  
proteases, lipid mediators



MC-B cooperation in resistance to secondary  
infestation with feeding exoparasites (e.g., ticks) .



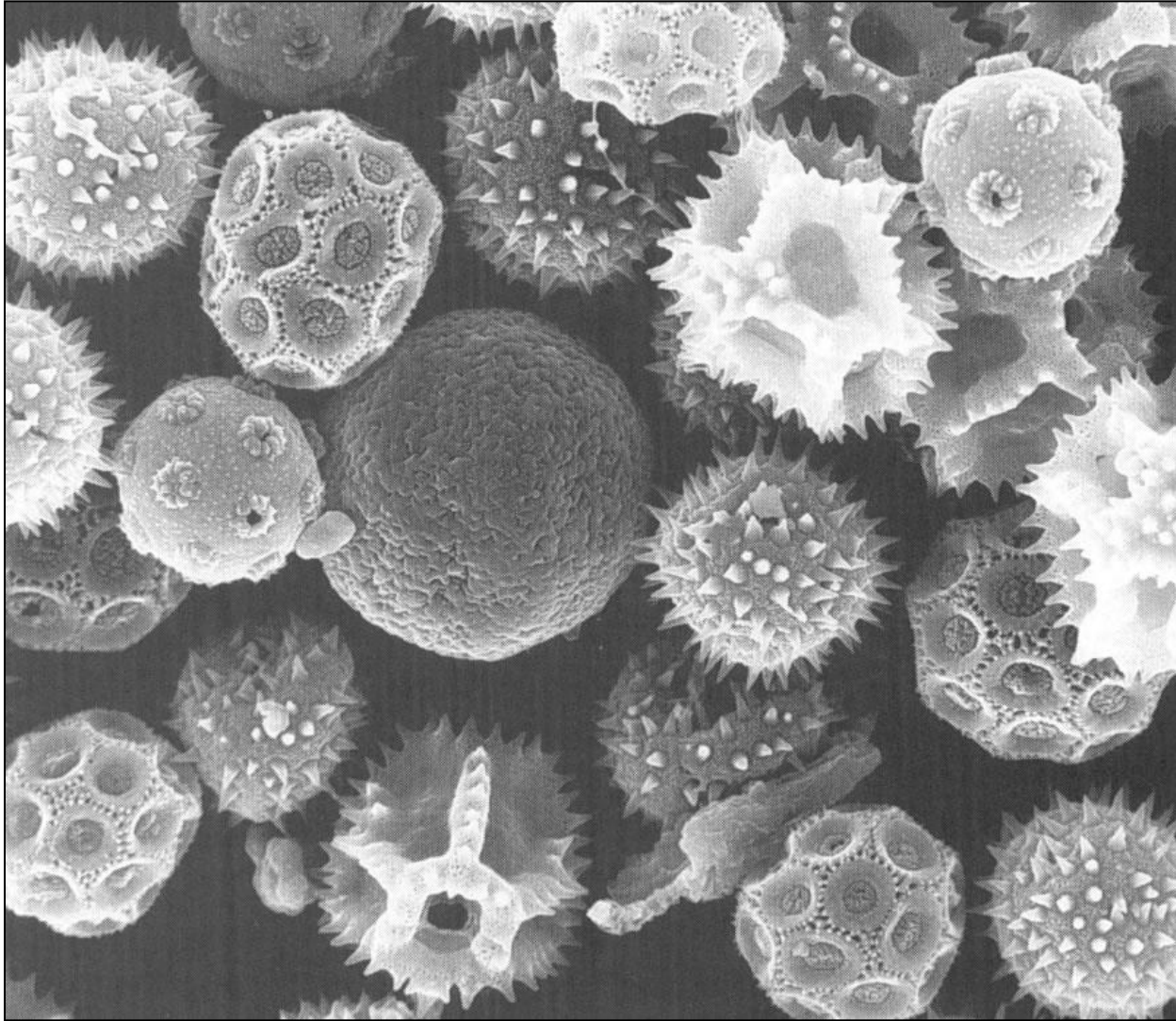
# Meest voorkomende allergenen

- Huisstofmijt
- Boom- en graspollen
- Katten- en hondenhaar
- Voedingsallergenen (pindanoot, soja)
- Schimmelsporen
- Beroepsgebonden (plasticindustrie)
- Medicijnen (antibiotica)
- Kakkerlak
- ...

# Huisstofmijt (*Dermatophagoides pteronyssinus*)



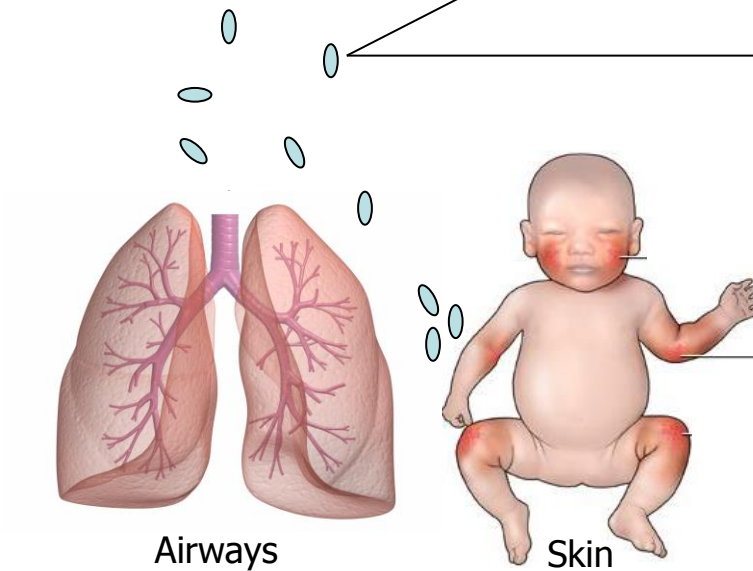
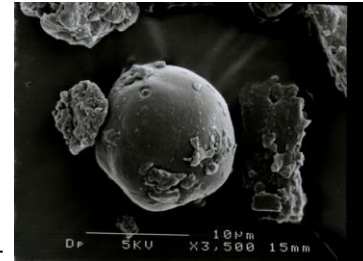
# Boompollen



Hoe onderzoeken we het  
ontstaan van allergie ?



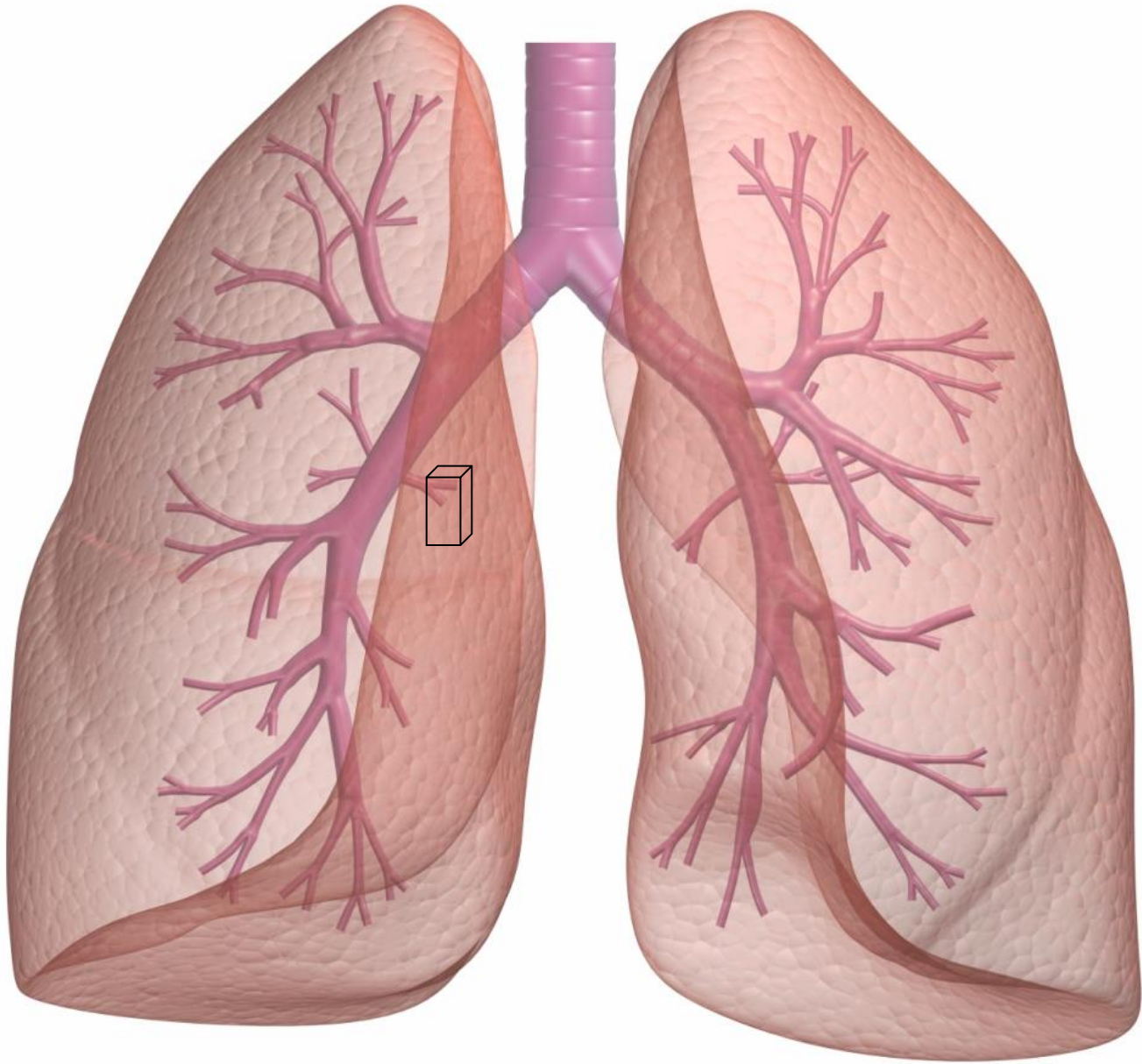
## House dust mite allergy

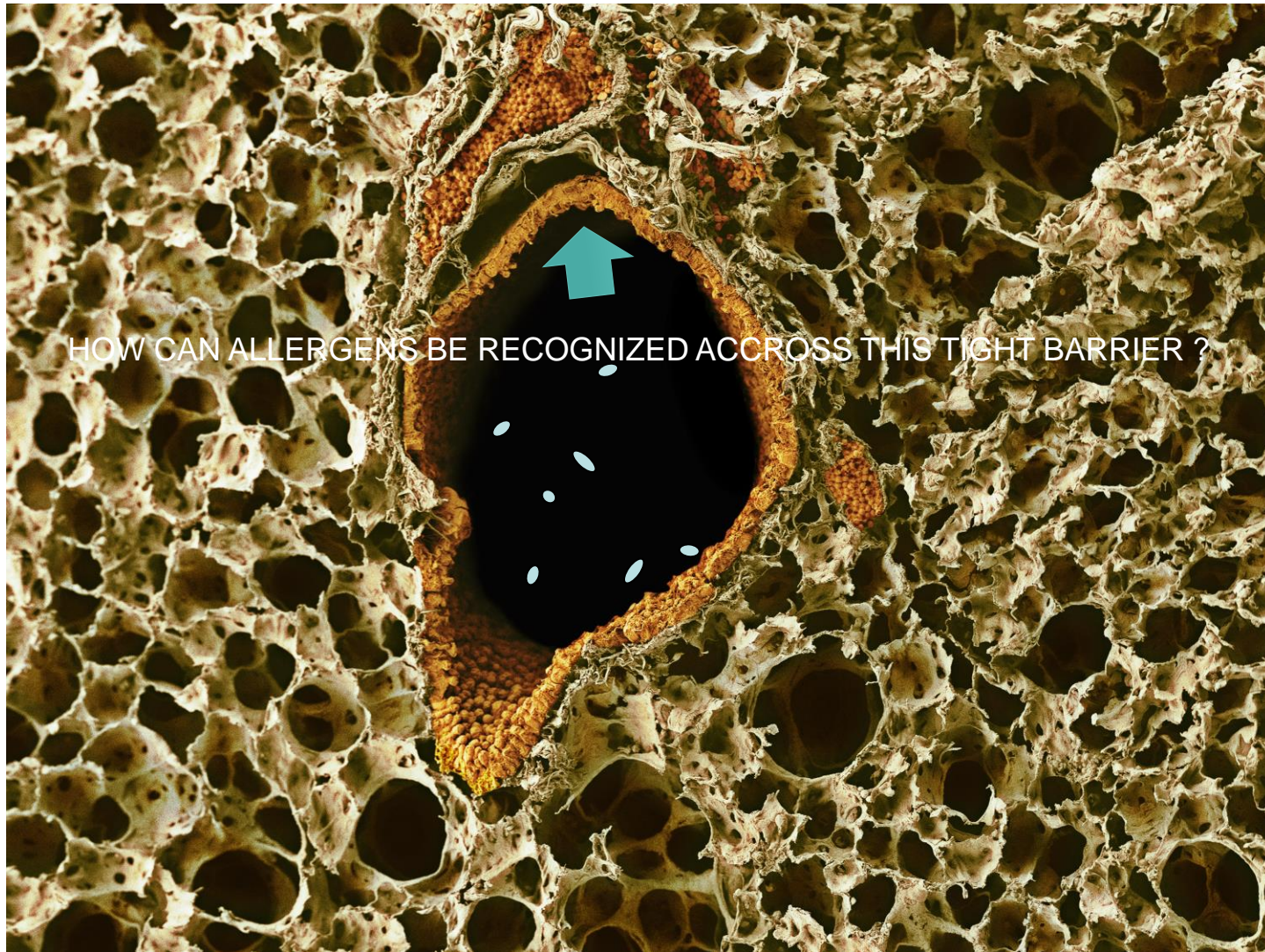


### House dust mite fecal pellets

- multiple "allergens"
- Der p 1, 2, 23 are major allergens
- some are cysteine proteinases
- contaminated with endotoxin from bug's GI tract



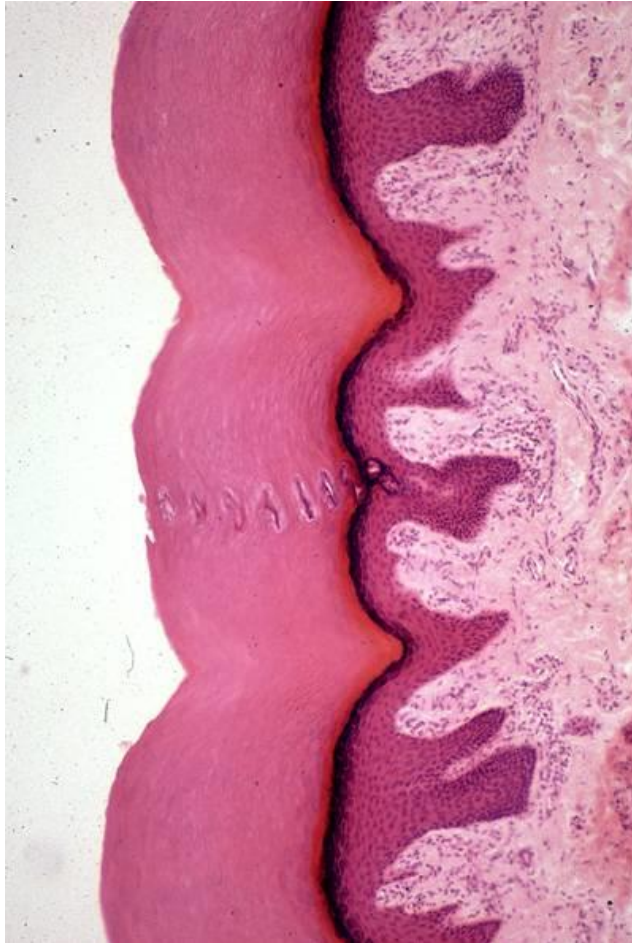




HOW CAN ALLERGENS BE RECOGNIZED ACCROSS THIS TIGHT BARRIER ?



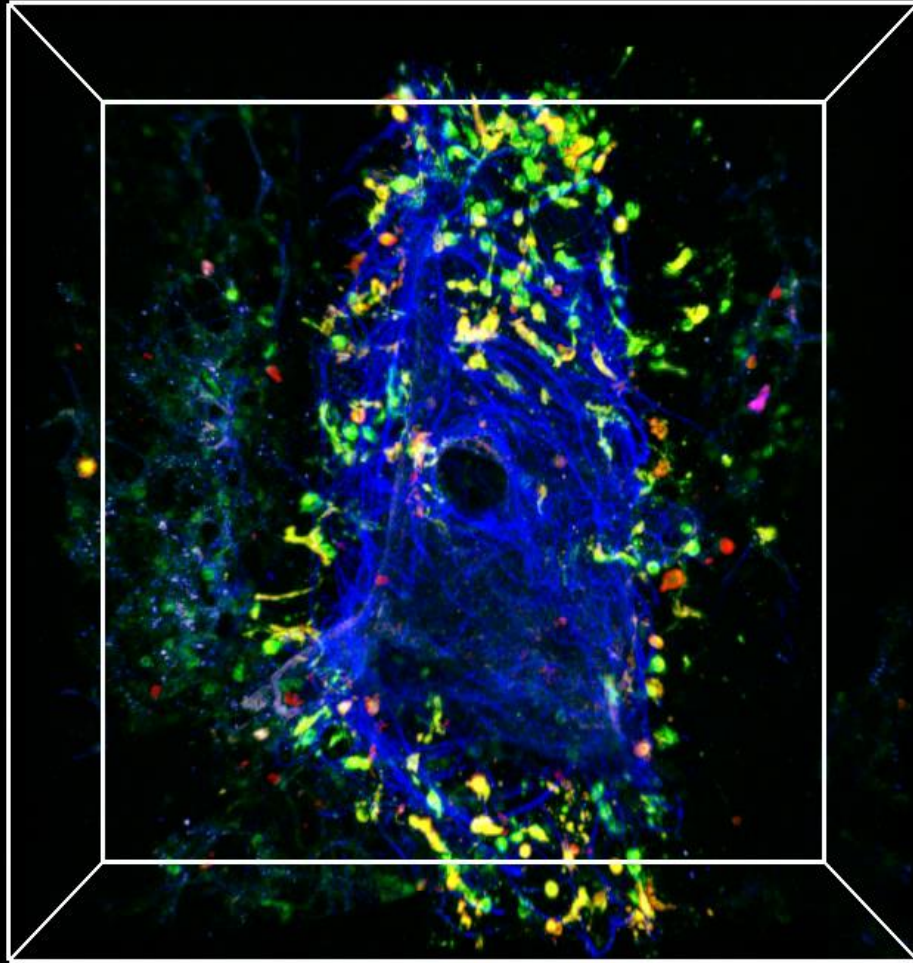
Skin/mucosae



Mur de la Peste



Genetica bepaalt hoe goed de barriere werkt !

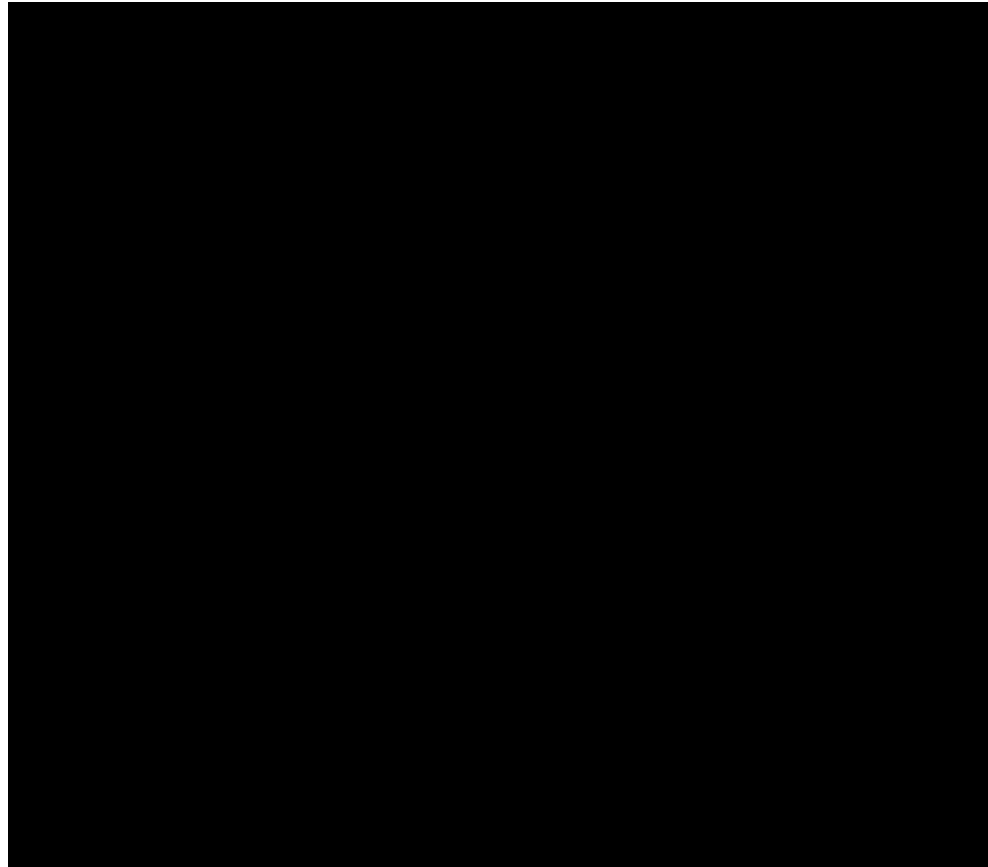


00

DCs-green + injected antibody to CD11b-red

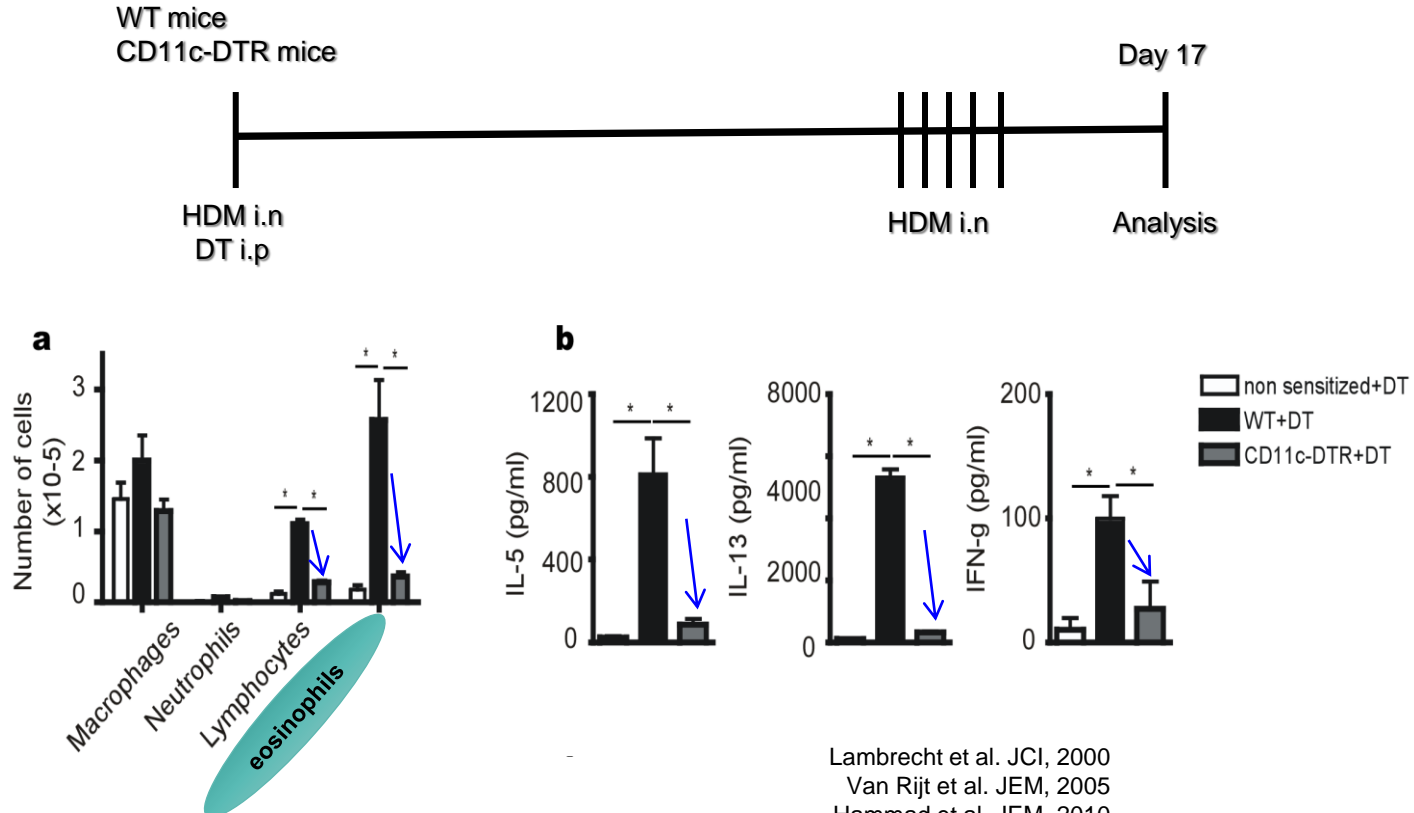
Movie by Melanie Matheu

## DCs probe the mucosa for incoming antigen






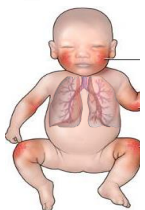
## DCs zijn nodig en voldoende om allergie aan HDM uit te lokken via de longen en de huid



Lambrecht et al. JCI, 2000  
 Van Rijt et al. JEM, 2005  
 Hammad et al. JEM, 2010  
 Plantinga et al. Immunity, 2014  
 Deckers, JACI, 2017

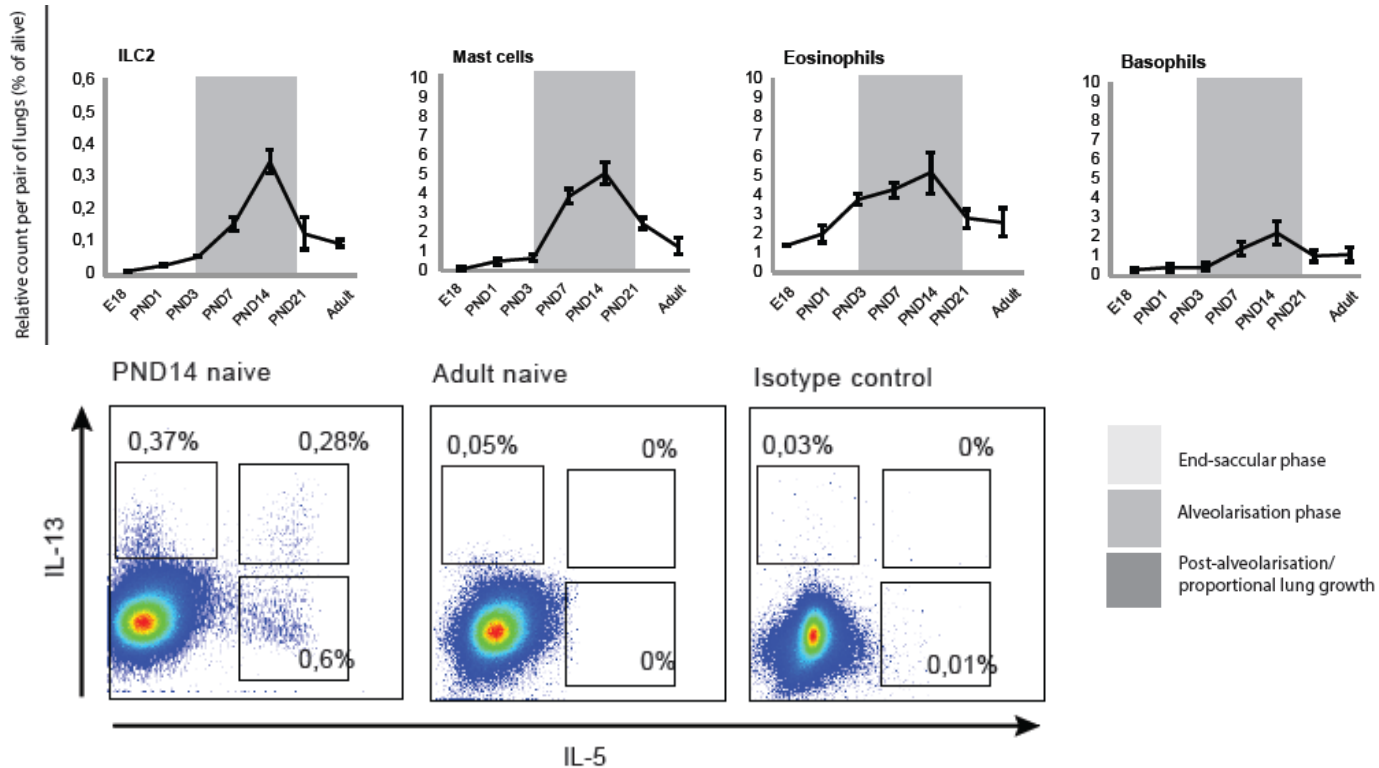
## Allergic sensitization to aeroallergens at young age coincides with postnatal lung development



		Embryonic	Pseudoglandular	Canalicular	Saccular	Alveolar
<b>Mouse</b>		E9-12	E12-15	E15-17	E17-birth	Birth-PND21
<b>Human</b>		Wk 3-7	Wk 7-16	Wk 16-26	Wk 26-36	Birth-3yrs

De Kleer I, Immunity, 2016

## Spontaneous type 2 immunity during alveolarisation phase !



De Kleer I, Immunity, 2016

# Hoe raken DCs geactiveerd na allergeen inhalatie?

## Allergens

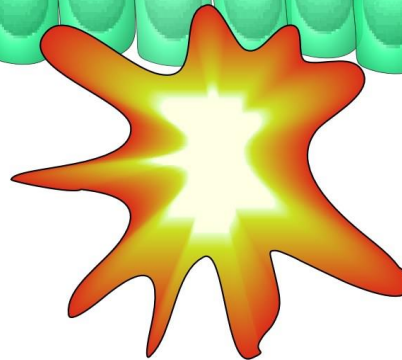
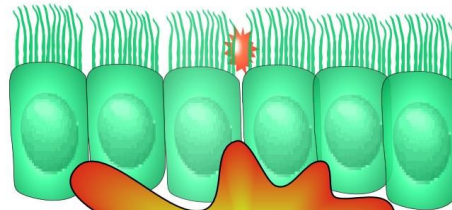
house dust mite  
pollen, dander

## Pathogens

virus  
bacteria

## Pollutants

cigarettes  
diesel  
ozone  
,...



## PATTERN RECOGNITION

Toll like receptors  
Nod like receptors  
Rig like receptors  
Protease act. receptors  
....

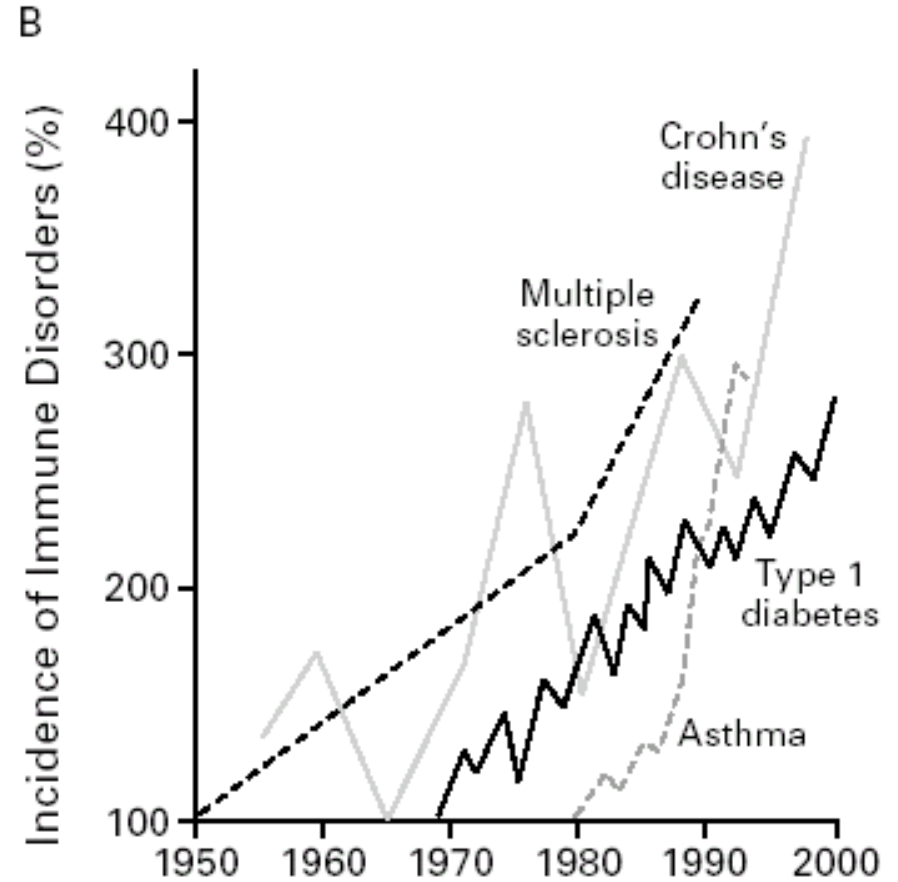
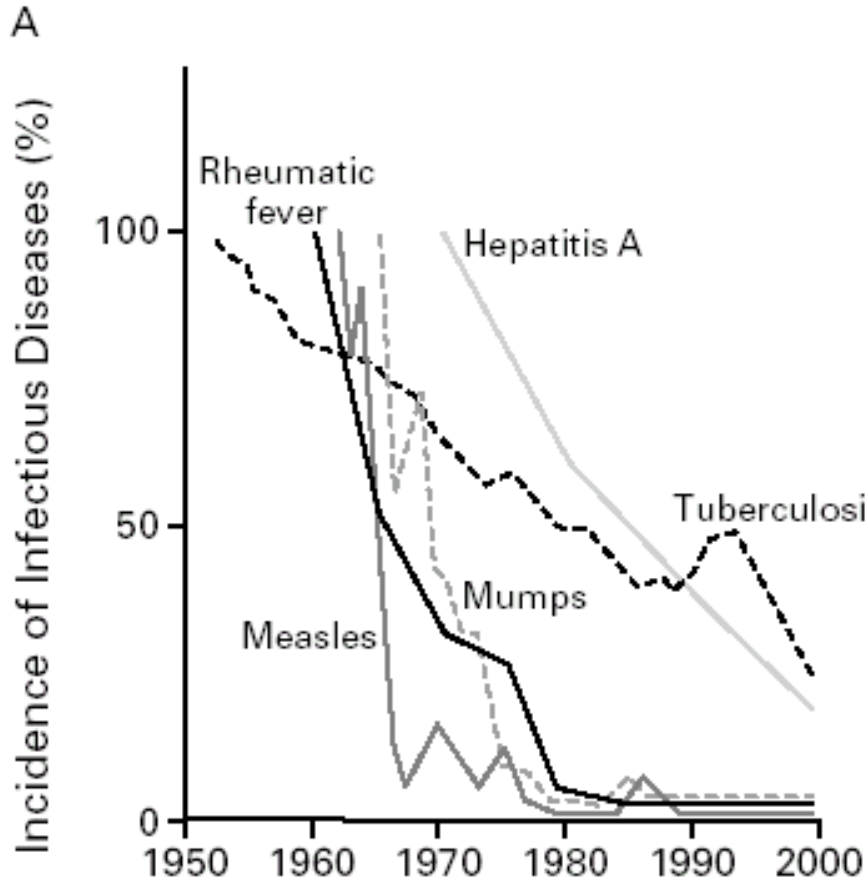
## 'STRESS' RESPONSES

oxidative stress  
hypoxia adaptation  
metabolic alterations  
> protein synthesis  
cytoskeletal changes  
....

Toename van allergie en  
astma ?



# Astma neemt enorm toe sinds WOII

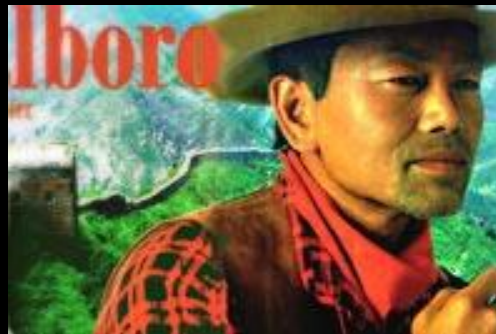


1/3 kinderen zijn allergisch  
1/8 kinderen hebben astma  
Wereldwijd 700 miljoen allergiepatiënten

# Luchtvervuiling ?



# Toegenomen roken ?



# De val van de Berlijnse muur brengt duidelijkheid





# Luchtvervuiling



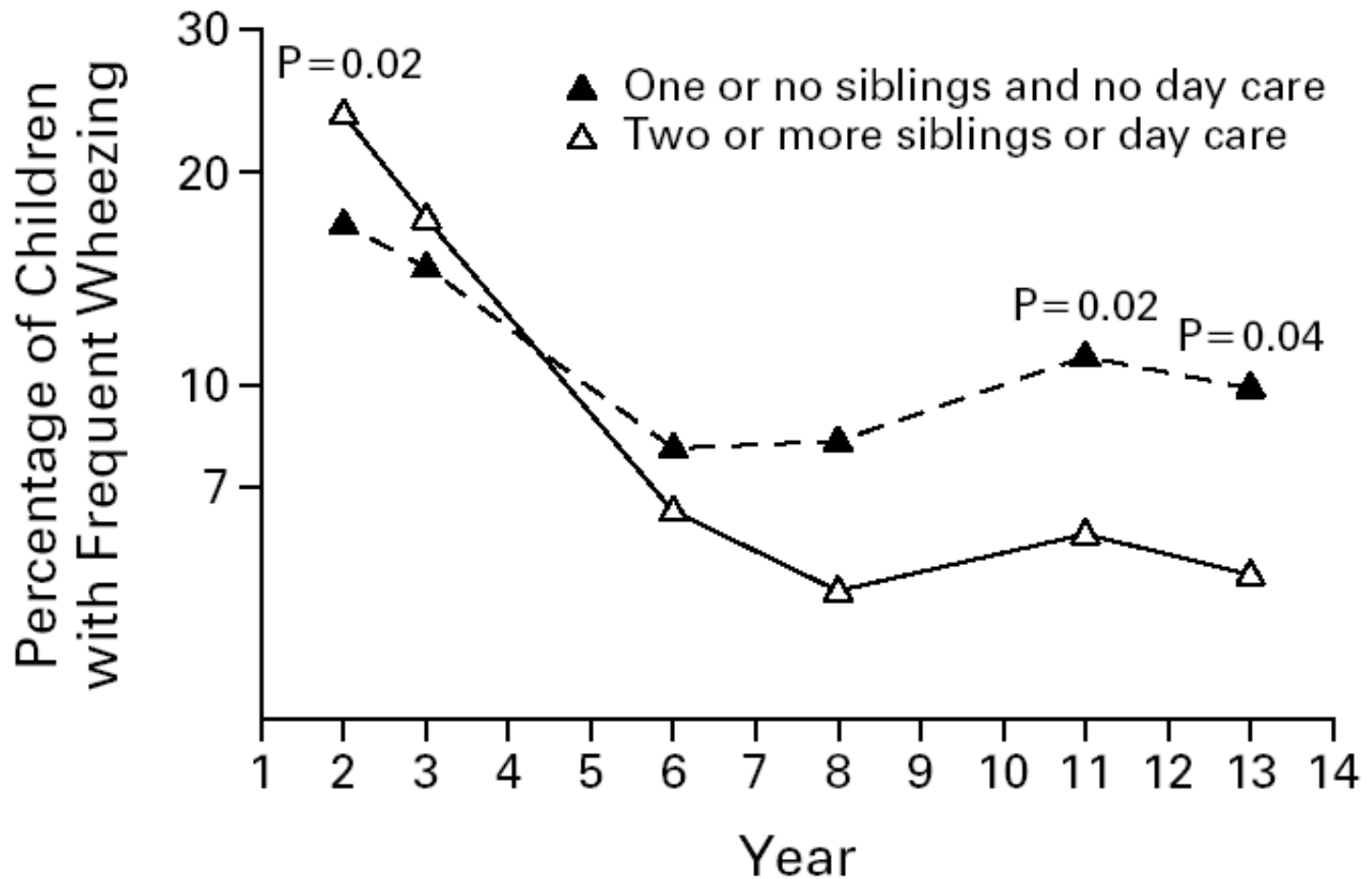
Leipzig



München

Allergie

# Invloed van verblijf in een creche (<6 m oud) Op symptomen van asthma op latere leeftijd



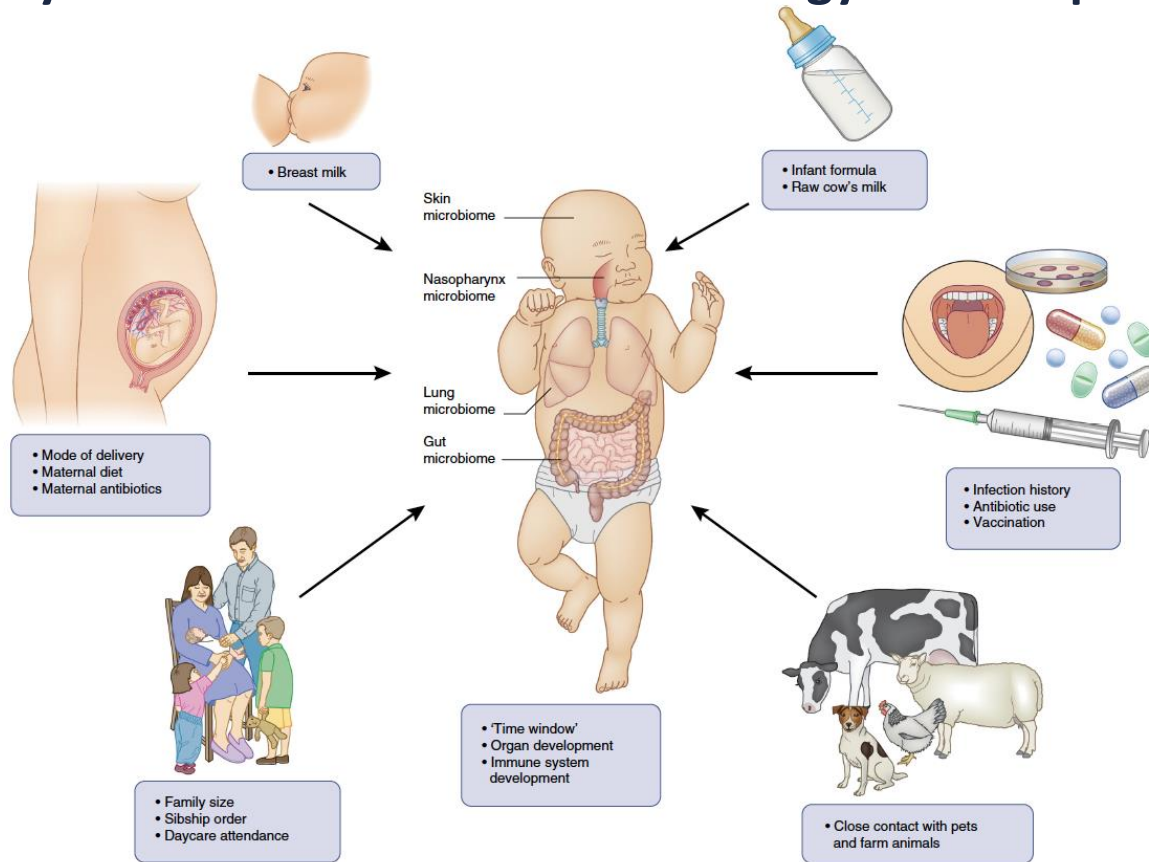


Old McDonald had a farm...but no asthma



Foto : Levien Willemse

# Early life factors associated with allergy risk and protection

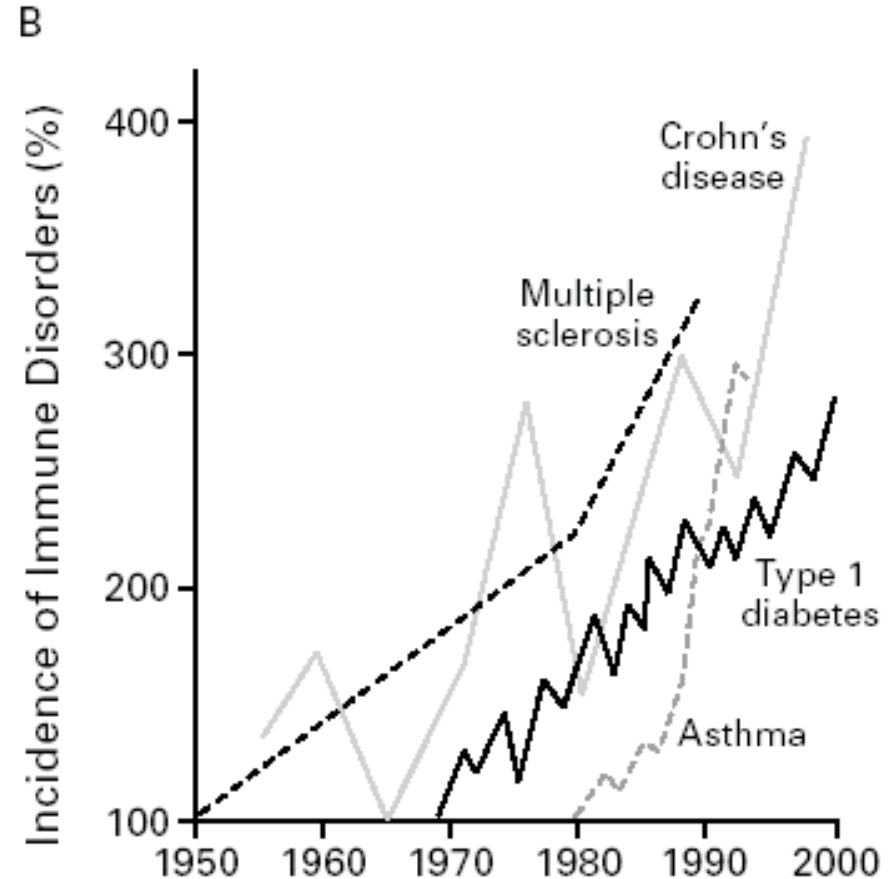
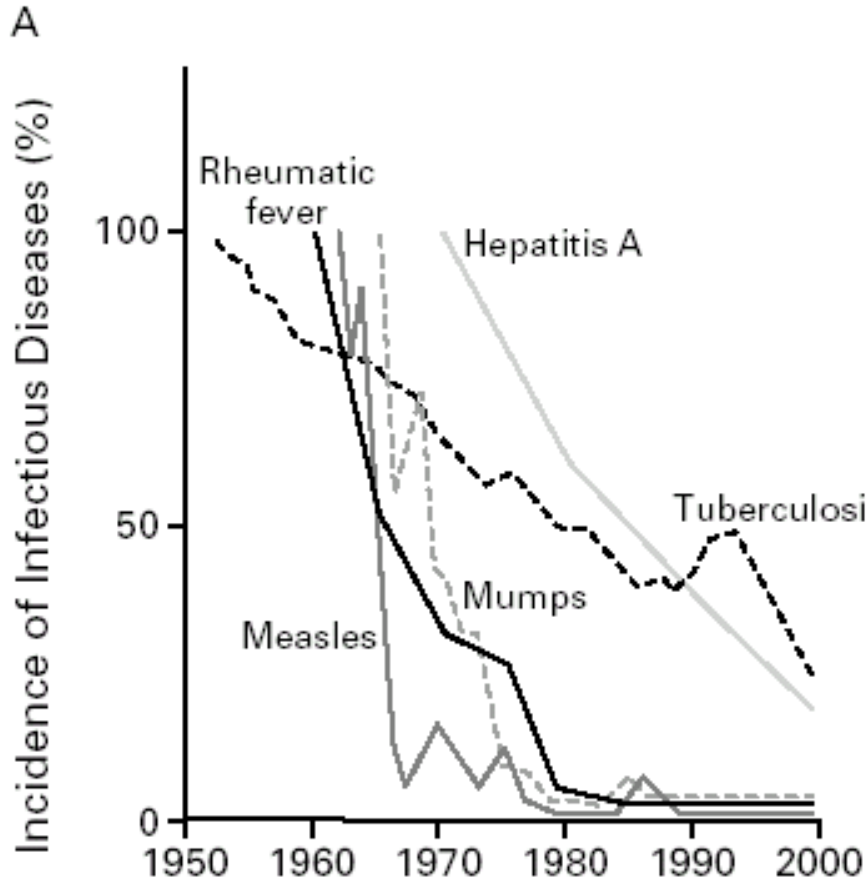


Debbie Maizels/Springer Nature

Lambrecht & Hammad. *Nature Immunol* 2017  
 Schuys et al. *Science* 2015



# Astma neemt enorm toe sinds WOII IS ER EEN CAUSAAL VERBAND ?

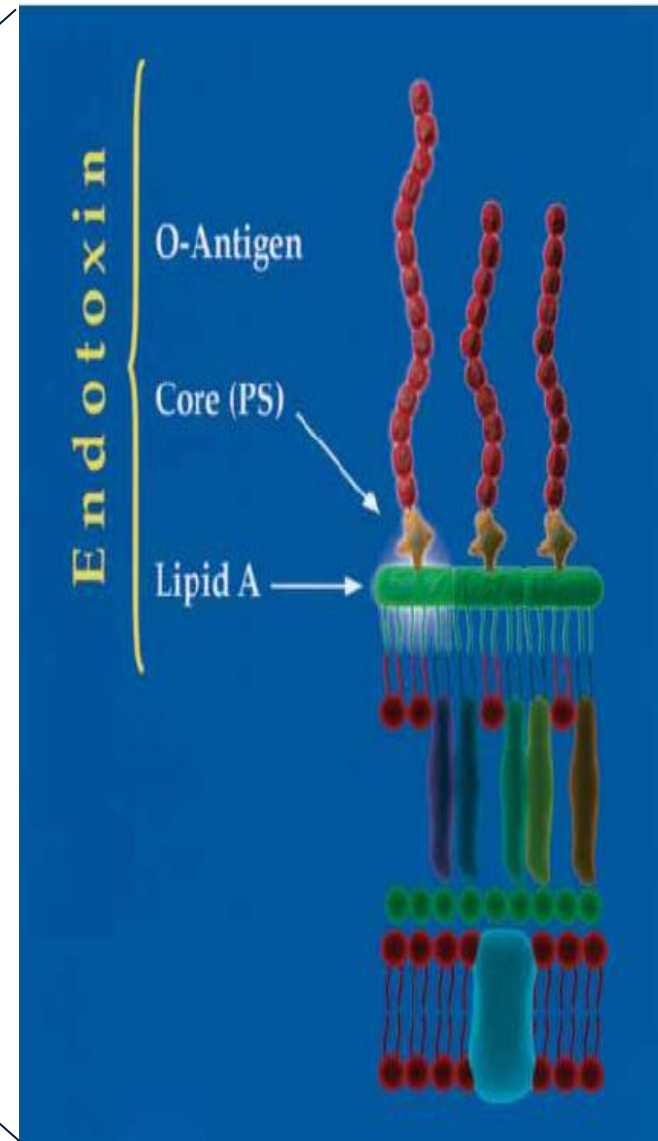
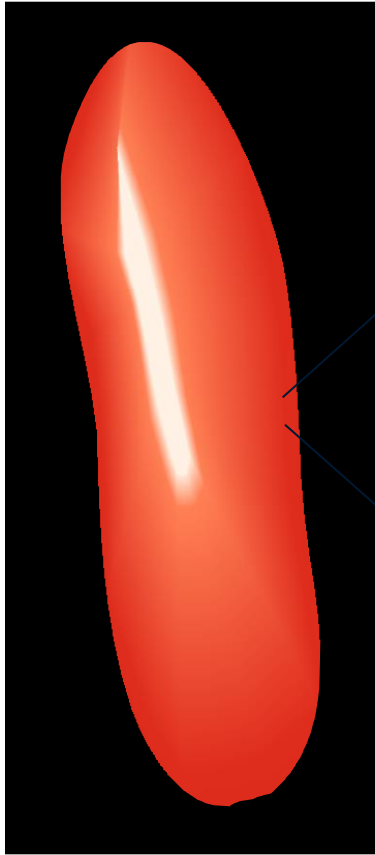


1/3 kinderen zijn allergisch  
1/8 kinderen hebben astma  
Wereldwijd 700 miljoen allergiepatiënten

# Nauw contact met dieren in eerste levensjaar telt!



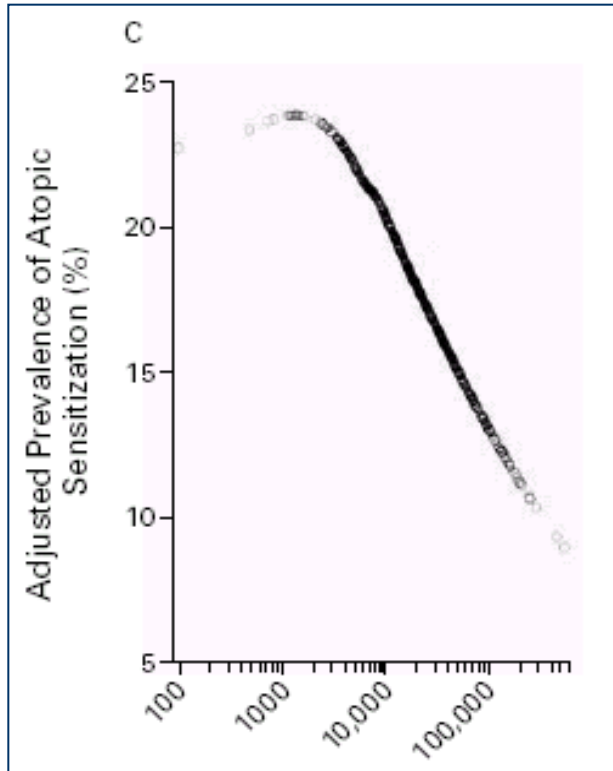
**There are a lot of bacterial derived products  
in stables and barns**



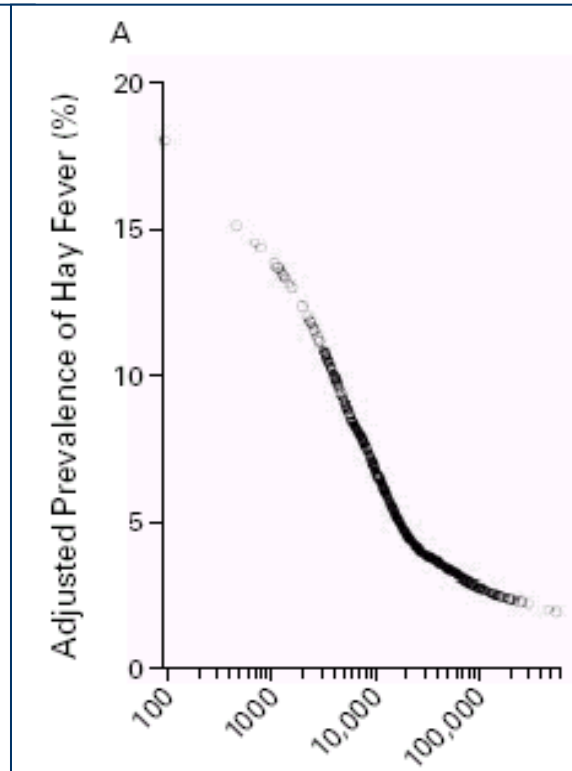
**Potential “asthma vaccines”**

# Exposure to LPS in 6-13 year old children and prevalence of sensitization and atopic diseases

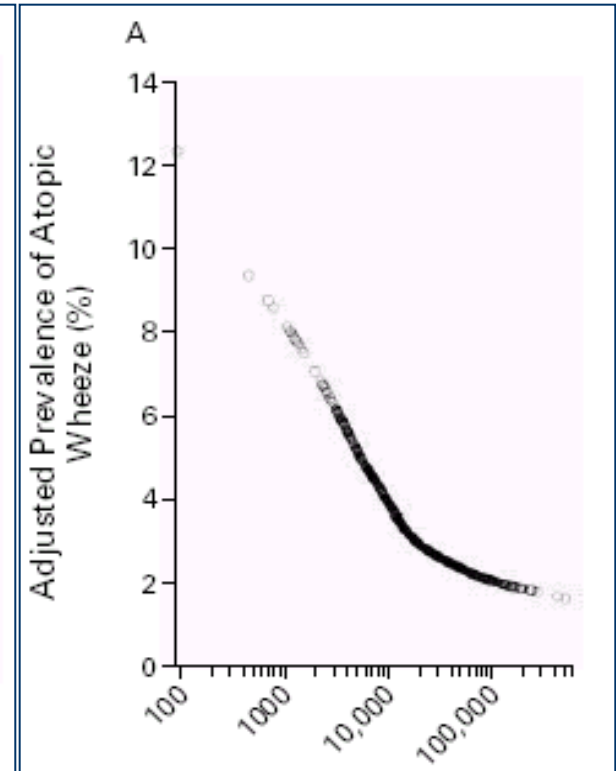
IgE sensitization



Hay fever



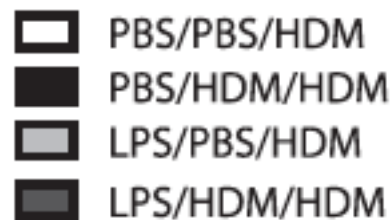
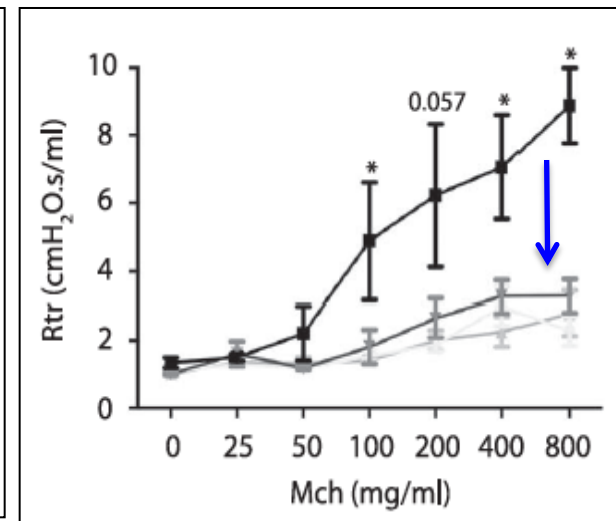
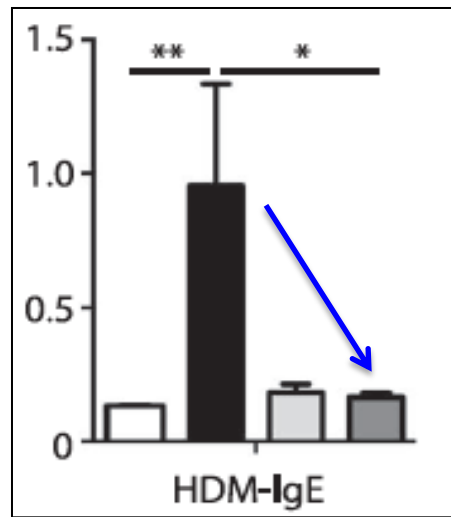
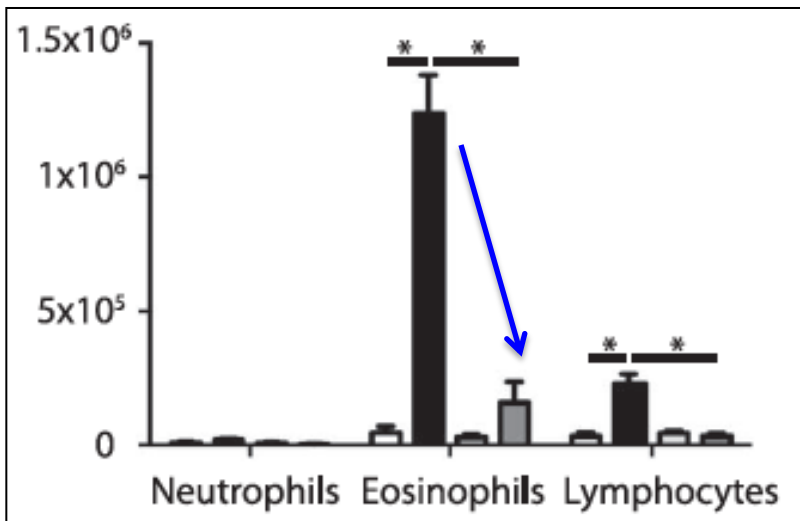
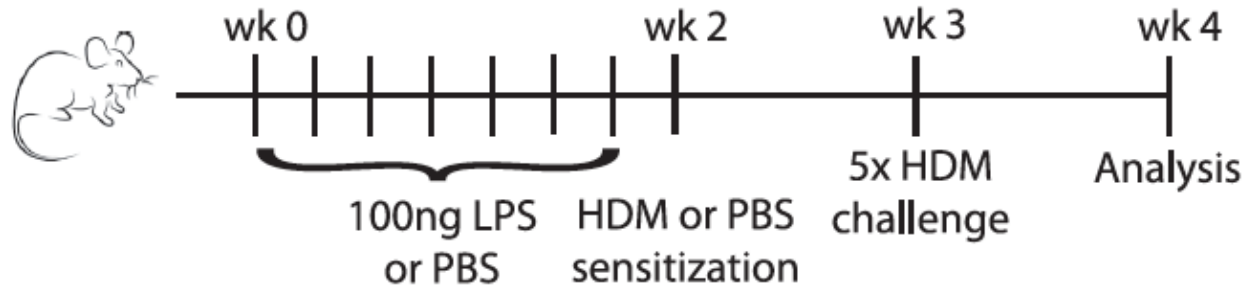
Atopic wheeze



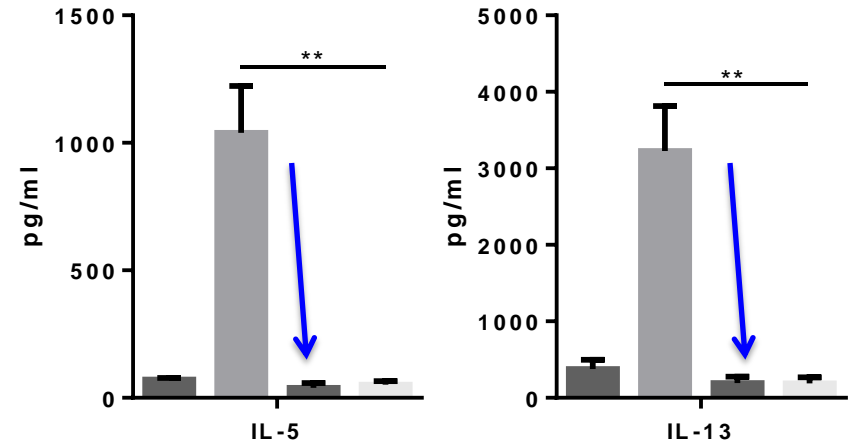
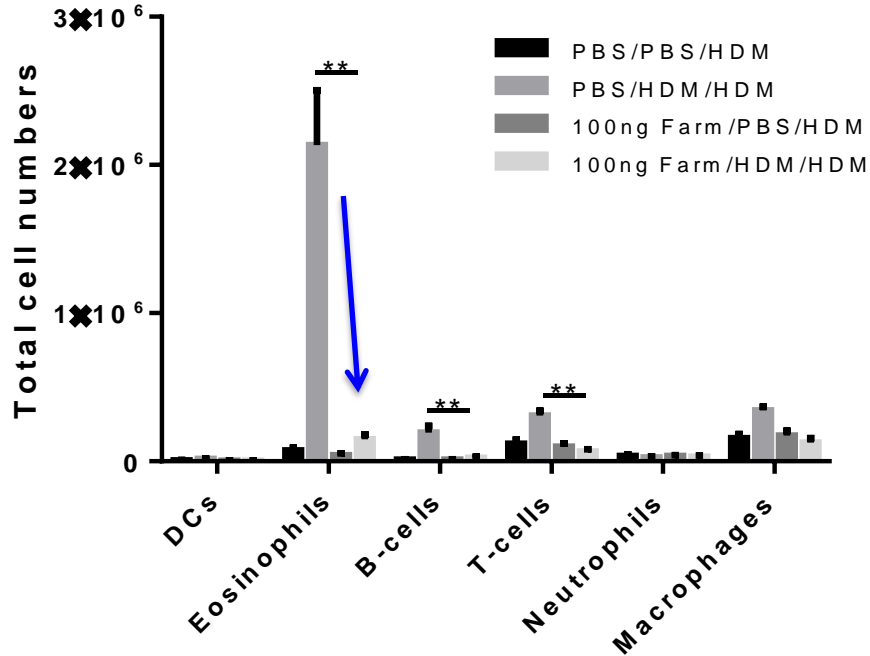
Endotoxin load in mattresses (U/m<sup>2</sup>)



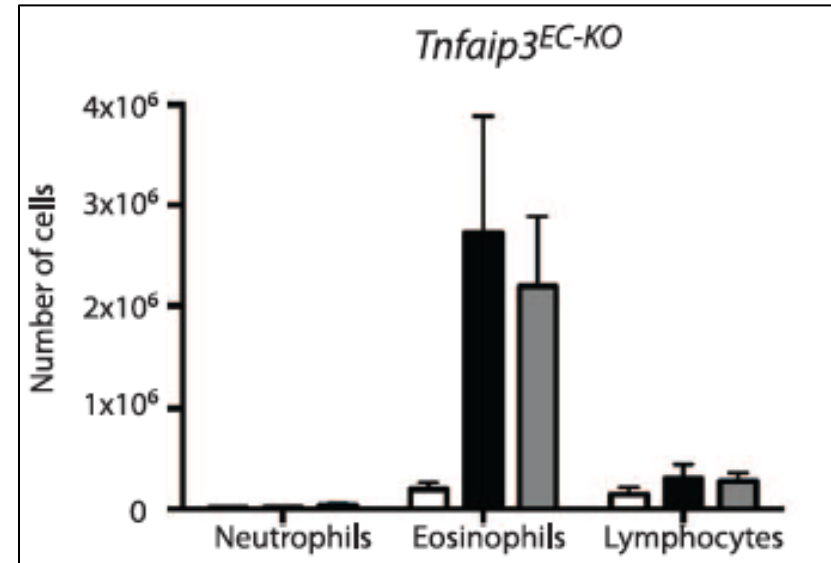
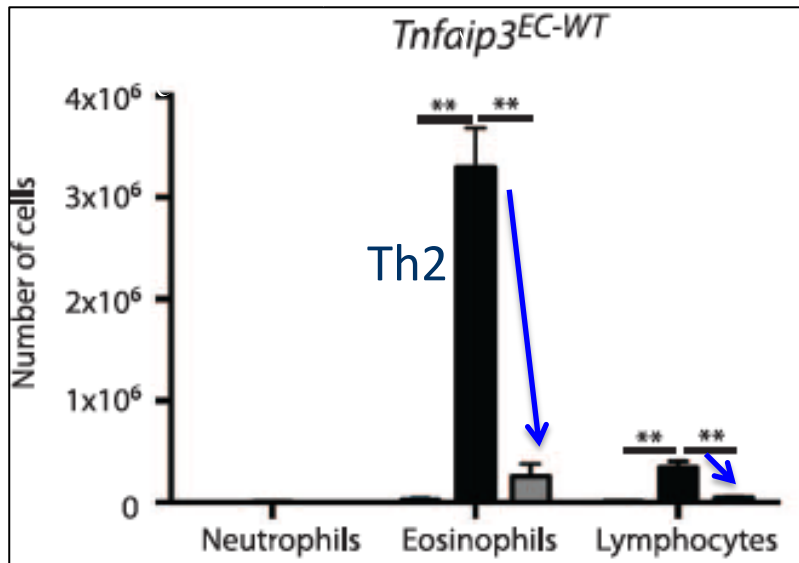
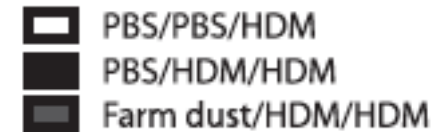
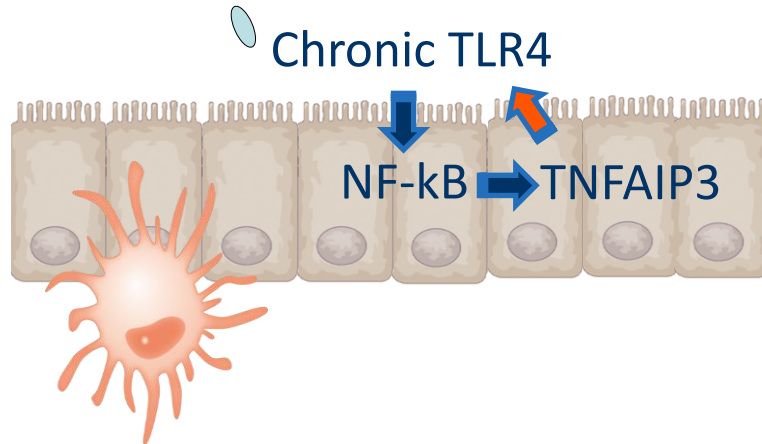
# Chronic low dose LPS exposure prevents HDM-induced asthma



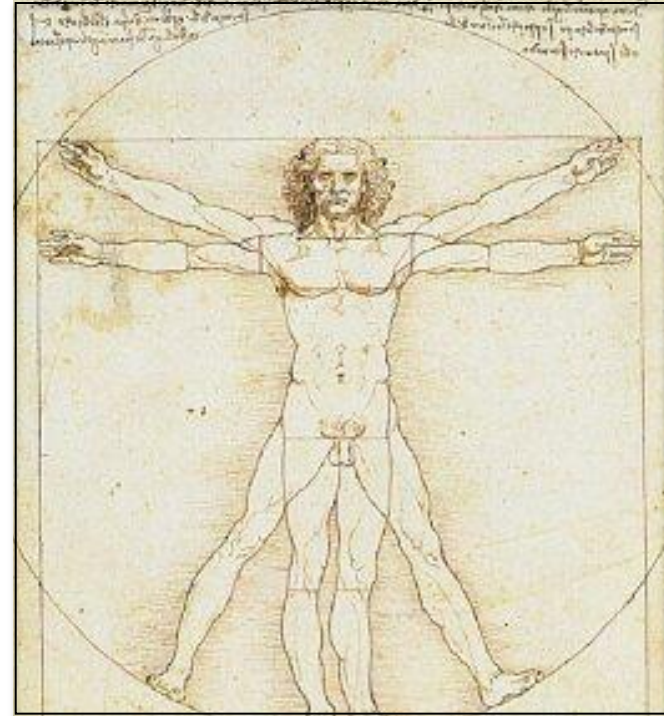
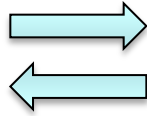
# Chronic low dose farm dust exposure prevents asthma and Th2 cytokine production in mice



# Farm dust exposure suppresses asthma via induction of the deubiquitinase TNFAIP3 in epithelial cells



**Be as translational as possible...**



**“A model is a lie that helps you see the truth”**

-Howard Skipper-

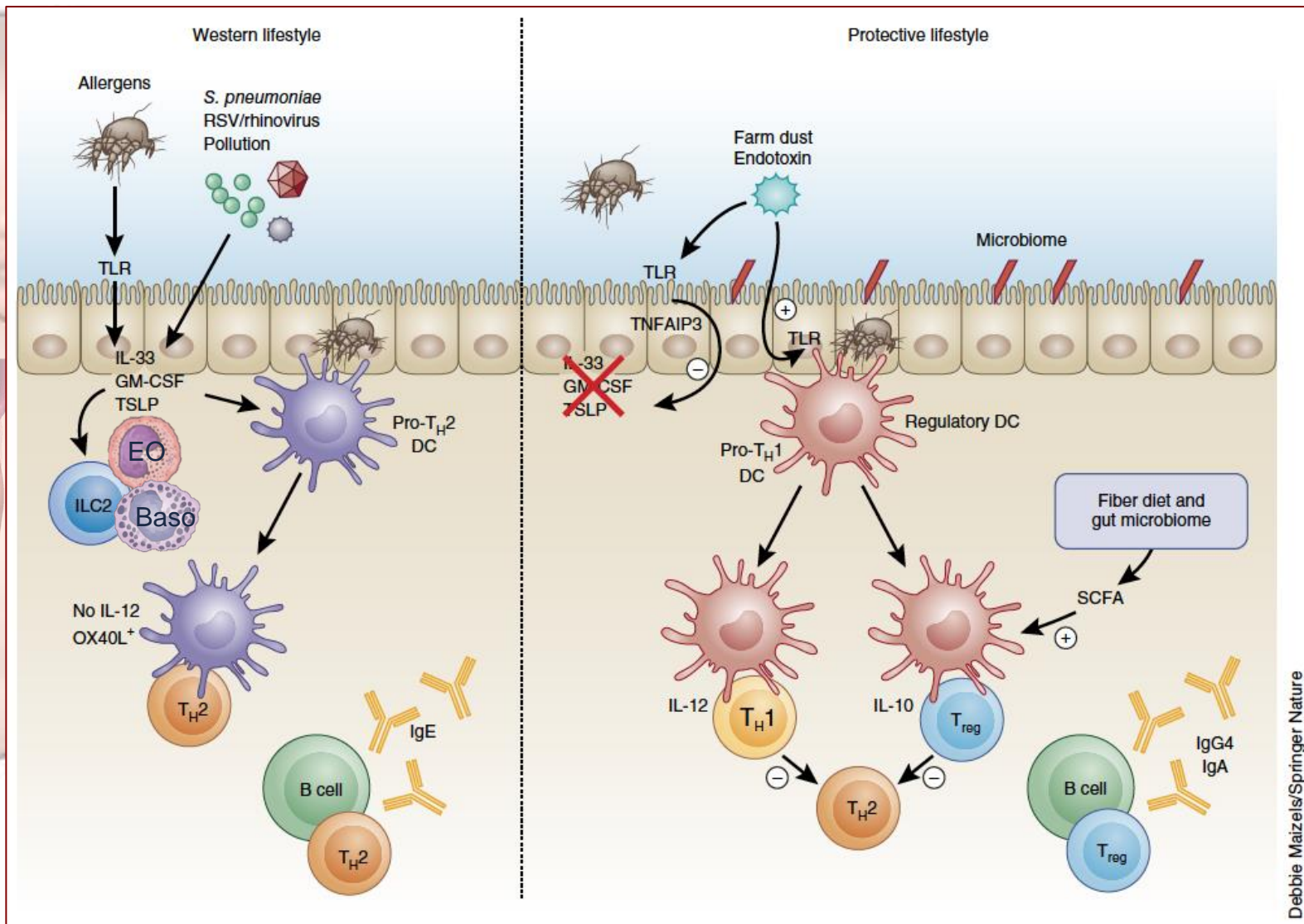


Kinderen die opgroeien op een boerderij en die toch niet beschermd zijn hebben een variant van het A20 gen



# What determines a “healthy” immune response to allergens in early life ?

## Think of the epithelium, the first line of defence !



Debbie Maizels/Springer Nature

# Life-style adviezen ?

- Mag of moet ons (klein)kind naar de creche als het ziek is ?
- Moet de creche niet wat minder schoon zijn ?
- Moeten we terug naar het platteland ?
- Moeten we wel zo snel antibiotica geven ?
- Moeten we onze kinderen wel vaccineren ?
- Moeten de huisdieren weg of juist niet ?



**In de toekomst zullen we moeten uitzoeken  
hoe we best het effect van microbiële opvoeding  
van ons immuunsysteem nabootsen**

